REMARKS

Applicants wish to thank Examiner Wilder and Examiner Zitomer for their courtesy extended in granting a personal interview in this case held on May 31, 2001, and for their kind consideration and helpfulness in reviewing the proposed new claims. Applicants have canceled previously pending claims 1-14 and have added new claims 15-55. Therefore claims 15-55 are currently pending.

The invention

Applicants have invented diagnostic test kits and as probes for hybridization, or for use as primers for determining mutations, especially deletions of relatively large stretches of nucleotides in genes associated with hereditary types of cancer, particularly in the BRCA1 gene. The probes are complementary to at least one stretch of nucleotides of the target gene in the sense or the anti-sense direction and may be used in various detection methods, such as hybridization or polymerase chain reaction (PCR) methods.

The probes may flank one or both sides of a deletion and in certain embodiments may comprise a fusion of two sequences adjacent to the site of a deletion of a stretch of nucleotides, such as for instance, between two ALU-elements of the BRCA1 gene. Probes that detect deletions of at least a major part of any one or all of exons 13, 14, 15 and16, or at least a major part of exon 22 are disclosed.

The probes of the invention are useful for detecting the presence of breast cancer and for detecting predisposition for breast cancer. In particular, the probes may be used in the detection of deletions that cause frame shift mutations, termination mutations or deletions of a stretch of nucleotides between two ALU-elements.

Finally, the invention also provides a method for determining the presence of a deletion of a stretch of nucleotides derived from the BRCA1 gene in a sample by contacting a sample with at least one probe which alone or together with a second means for detecting a deletion within the BRCA1 gene, allowing hybridization to occur and detecting the hybridization product.

The rejections based on 35 U.S.C. §112 raised in the Office Action of December 6, 2000

In the office action of December 6, 2000 the Examiner recited several grounds of rejection based on 35 U.S.C. §112, second paragraph each of which is addressed below.

At paragraph 4a of the office action, claims 1-11 were rejected as allegedly indefinite for the recitation of "a means." According to the Examiner, the term "a means" is not properly defined in the specification and one of ordinary skill would not recognize the scope of the claimed invention.

In response, Applicants assert that the term "a means" is in fact clearly defined in the specification and the skilled artisan would indeed appreciate the scope of the claims. The specification is replete with examples of the use of "a means" for detecting deletions of a stretch of nucleotides from a BRCA1 gene. For example, at page 6, lines 3-15 of the specification, several hybridization-based and PCR-based probes are disclosed as suitable means for detecting a deletion of a stretch of nucleotides from a BRCA1 gene in a sample.

From these and other examples provided in the specification, the skilled artisan would readily appreciate these and other suitable means for detecting a deletion of a stretch of nucleotides from a BRCA1 gene in a sample. Therefore, Applicants believe that the term "a means" as applied in the claims is clear and definite, and respectfully requests that this rejection be withdrawn.

At paragraph 4b of the office action, claims 6-12 were rejected as allegedly indefinite for the recitation of "anyone" of the aforegoing claims.

In response, Applicants have cancelled claims 6-12 and added new claims 15-55, none of which recite the offending language. Therefore, Applicants respectfully request that this rejection be withdrawn.

At paragraph 4c, claims 7-13 were rejected as allegedly indefinite for the recitation of "major part" as applied to the specified exons or sequences. According to the Examiner, the

term is not defined in the claim nor is a standard for ascertaining the requisite degree provided in the specification. Further, the Examiner states that one of ordinary skill would not recognize the scope of the invention.

In response, Applicants assert that the term "major part" has its usual and customary meaning, i.e. more than 50% of the whole. See the only applicable definition (2) of "major *adj*" in Meriam Webster's Ninth New Collegiate Dictionary, 1990, Meriam Webster Inc., Springfield, MA. Definition 2: The adjective "major" is defined as: "greater in number, quantity or extent <the ~ part of his work>"(Attached as Exhibit 1).

As applied to the present specification and claims, the usual and customary meaning of "major part" clearly refers to the greater part in number of nucleotides (i.e. quantity or extent) of the nucleotide sequence to which it refers. Therefore, Applicants assert that the term "major part" is clear and definite and allows the skilled artisan to recognize the scope of the claimed invention and respectfully requests that this rejection be withdrawn.

At paragraph 4d of the office action, claim 8 was rejected as allegedly indefinite for lack of antecedent basis in the recitation "nucleotides 1396-1662."

In response, Applicants have cancelled claim 8 and added new claims 15-55, none of which recite the offending language. Therefore, Applicants respectfully request that this rejection be withdrawn.

At paragraph 4e, claim 14 was rejected as allegedly indefinite for the recitation of "other means." According to the Examiner, the term "other means" is not defined in the specification or claims and it cannot be determined to what Applicant is making reference.

In response, Applicants have cancelled claim 14 and added new claims 15-55, none of which recite the term "other means." Therefore, Applicants respectfully request that this rejection be withdrawn.

At the second paragraph labelled as 4d (sic), the Examiner alleges that claim 14 is confusing in that it recites "is capable of" because it cannot be determined whether "capable of" is a property of the probe or of the said "other means." The Examiner goes on to suggest changing "is capable of distinguishing" to "which distinguishes."

In response, Applicants respectfully point out that claim 14 has been canceled and none of the new claims, 15-55 recite the "capable of" language. Therefore the rejection is moot and should be withdrawn, which action is respectfully requested.

At paragraph 4f, claim 14 the Examiner alleged that the recitation of "identifying the hybridization product" lacked proper antecedent basis because the hybridization conditions have not been identified and the prior steps do not indicate that hybridization has taken place.

Further, the Examiner stated that the term "possible" is unclear in the context of the language used in claim 14.

In response, Applicants point out that claim 14 has been canceled and the corresponding new claim (claim 55) clearly recites the proper antecedent basis for "identifying the hybridization product" and nowhere incorporates the term "possible." The rejection is therefore moot. Applicants respectfully request that this rejection be withdrawn.

The rejections based on 35 U.S.C. §102 raised in the Office Action of December 6, 2000

At paragraph 6 of the office action the Examiner rejected claims 1-3 and 14 as allegedly being anticipated by Skolnick et al. (EP 0 699 754 A1, published on March 6, 1996) under the patent statutes at 35 U.S.C. §102(b).

According to the Examiner, Skolnick et al. teach a method and kit for detecting predisposition to breast and ovarian cancers, wherein the diagnostic techniques include detection of mutational events of the BRCA1 locus involving deletions, insertions and point mutations within the coding sequences and non-coding sequences of the genes, thereby anticipating the invention of claim 1.

Further, the Examiner states that the inventions of claims 2 and 3 are anticipated by the Skolnick et al. teachings of a kit comprising at least one probe for hybridization, and of a kit comprising the necessary elements for Southern blotting, respectively.

Lastly, the Examiner states that the invention as recited in claim 14, drawn to a method for determining the presence in a sample of a nucleic acid derived from a BRCA1 gene having an alteration, wherein said alteration is a deletion, comprising contacting said sample with at least one probe capable of distinguishing between BRCA1 genes having the alteration and genes not having the alteration, allowing for hybridization between said probe and nucleic acid and identifying the hybridization product, according to the present application, is anticipated by the recitation of claims 1-9 and 22 of the Skolnick et al. reference.

In response, Applicants point out that claims 1-3 and 14 have been canceled and new claims 15-55 have been added. The new claims 15, 16 and 17 correspond to original claims 1-3 respectively, and claim 55 corresponds to original claim 14. Each of these new claims recites the limitation that the deletion to be detected comprises at least a major part of any one or all of exons 13, 14, 15, and 16, or at least a major part of exon 22.

Skolnick et al. relates to methods and materials used to detect a human breast and ovarian cancer predisposing gene (BRCA1) – See Abstract. However, the Skolnick et al. reference does not disclose the specific deletions of the BRCA1 gene recited in claims 15-55 of the present invention. Even more importantly, Skolnick et al. could not have detected the deletions that are detected by the presently claimed methods because "Such mutations are difficult, if not impossible, to detect by the current[ly] PCR-based approach (if their

occurrence or the site thereof is unknown) using genomic DNA as template, which has been most widely applied to establish the current mutation spectrum of BRCA1." (present specification at page 5, line 32-page 6, line 2). The present specification provided the first disclosure of the existence and detection of the specific deletions as recited in claims 15-55. Therefore Skolnick et al. can not have anticipated, let alone enablingly taught, a probe for hybridization or the necessary elements for Southern blotting for a diagnostic kit according to the pending claims of the present invention.

In summary, nowhere in the Skolnick et al. reference is there any teaching of deletions of at least a major part of any one or all of exons 13, 14, 15, and 16, or at least a major part of exon 22. Applicants therefore assert that claims 15-55 are novel over Skolnick et al. and respectfully request that this rejection be withdrawn.

At paragraph 8 of the office action the Examiner rejected claims 1-5 and 11-14 as allegedly being anticipated by Swensen et al. (U.S. patent 6,150,514, with an effective filing date of April 9, 1997) under the patent statutes at 35 U.S.C. §102(e).

According to the Examiner, the Swensen et al. reference anticipates claim 1 in that it teaches a method and diagnostic kit for detecting the presence of predisposition to breast and ovarian cancers, whereby a means is provided for detecting a deletion of a stretch of nucleotides from a BRCA1 gene in a sample.

The Examiner also asserted that claims 2 and 3 are anticipated by the teachings of Swensen et al. of at least one probe for hybridization and the necessary elements for Southern blotting.

Further, the Examiner asserted that claims 4 and 5 are anticipated by the teachings of Swensen et al. of a probe comprising sequences complementary to sequences on both sides of the deletion in the BRCA1 gene and wherein the deletion comprises one or more exons.

Further still, the Examiner asserted that claim 11 is anticipated by the teachings of Swensen et al. of a deletion comprising a stretch of nucleotides between two ALU elements.

Yet further, the Examiner asserted that claims 12 and 13 are anticipated by the teachings of Swensen et al. of probes for use in a diagnostic kit comprising a nucleic acid sequence which is a fusion of two ALU elements of the BRCA1 gene.

Lastly, the Examiner asserted that claim 14 is anticipated by the teachings of Swensen et al. of a method for determining the presence in a sample of a nucleic acid derived from the BRCA1 gene having a deletion of a stretch of nucleotides, exactly as recited in claim 14.

In response, Applicants point out that claims 1-5 and 11-14 have been canceled and new claims 15-55 have been added. The new claims 15-24 and 31-54 correspond to original claims 1-5 and 11-13, respectively. Claim 55 corresponds to original claim 14. Each of these

new claims recites the limitation that the deletion detected comprises at least a major part of any one or all of exons 13, 14, 15, and 16, or at least a major part of exon 22.

Swensen et al. describes a 14Kb deletion, which removes the promoter region of BRCA1 and includes exons 1a, 1b and 2. There is no disclosure of a probe or diagnostic kit for detecting the presence of or predisposition for breast cancer, whereby a means is provided for detecting deletions comprising at least a major part of any one or all of exons 13, 14, 15, and 16, or at least a major part of exon 22, as recited in the pending claims. Therefore none of claims 15-55 are anticipated by the Swensen et al. reference. Applicants therefore respectfully request that this rejection be withdrawn.

The rejection based on 35 U.S.C. §103 raised in the Office Action of December 6, 2000

At paragraph 10 of the office action the Examiner rejected claims 1, 2 4-6 and 11-13 as allegedly unpatentable over Puget et al. (Cancer Research, published in March, 1997) in view of Ahern (The Scientist, July 1995) under the patent statutes at 35 U.S.C. §103(a).

According to the Examiner, the method for detecting predisposition to breast cancer of Puget et al. differs from that of the claimed invention in that Puget et al. do not teach a kit for practicing the method. The Examiner points to the Ahern article for the teaching that a kit provides convenience, time management and ease of practicing to the investigator. Therefore, the Examiner opines, it would have been ***prima facie*** obvious to one of ordinary skill in the art at the time the invention was made to have provided the method of detecting

predisposition to cancer as taught by Puget et al. in the form of a kit for overall convenience and ease of practicing as taught by Ahern.

In response, Applicants point out that claims 1, 2, 4-6 and 11-13 have been canceled and new claims 15-55 have been added. The new claims 15, 16 and 18-30 correspond to original claims 1, 2 and 4-6, respectively. Claims 31-54 correspond to original claims 11-13. Each of these new claims recites the limitation that the deletion to be detected comprises at least a major part of any one or all of exons 13, 14, 15, and 16, or at least a major part of exon 22.

Applicants assert that up until the time the present invention was made, the deletions of the BRCA1 gene comprising at least a major part of any one or all of exons 13, 14, 15 and16, or at least a major part of exon 22, detected by the currently claimed kits and probes, using the claimed methods, had not been disclosed, and more importantly were not predicted by the Puget et al. or by the Ahern references.

Thus, even if the cited references are combined, the combination falls short of the presently claimed invention. Therefore, Applicants respectfully request that the rejection for obviousness, based on the combination of Puget et al. in view of Ahern, be withdrawn.

Sequence Listing

The Office Action of December 6, 2000 contained a Notice to Comply with the Requirements for Patent Applications Containing Nucleotide Sequences and/or Amino Acid Sequence Disclosures. In response, Applicants have appended hereto an appropriately corrected SEQUENCE LISTING and Computer readable form (CRF).

Formal Drawings

The Office Action of December 6, 2000 also contained a Notice of Draftperson's Patent Drawing Review requiring new formal figures 1 and 3.

Applicant will provide appropriate drawings to correct these informalities at the time of allowance of claims from this application.

Support for new claims 15-55

New claims 15-55 are fully supported by the claims as originally filed and no new matter has been added by this amendment.

This Response is filed within six months of the December 6, 2000 Office Action. Accordingly, a Petition for a Three Month Extension of Time and the appropriate fee are filed concurrently herewith.

The assignee is a small entity. Therefore, the reduced fee for the extension of time is being submitted herewith.

If the Examiner has any questions relating to this Amendment or to this application in general, it is respectfully requested that the Examiner contact the Applicants' undersigned attorney at the telephone number provided below.

Respectfully submitted,

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VERSION OF AMENDMENT WITH MARKINGS TO SHOW CHANGES MADE

In the specification

At page 5 please replace the paragraph which begins at line 9 and continues to page 6 line 2 with the following divided paragraphs between which the heading "SUMMARY OF THE INVENTION" is inserted:

- - An intriguing feature of BRCA1, and unexpected in the light of Knudson's two-hit inactivation theorem for tumor suppressor genes, is that somatically acquired mutations are extremely rare in ovarian tumors [34-38] and have in fact not yet been detected in 135 breast tumors [39-40]. This might indicate that inactivation of BRCA1 is not selected for during tumorigenesis of the non-inherited form of breast cancer. BRCA1 expression might be critical only during certain stages of tissue development, e.g., during puberty when the breast undergoes its final differentiation into a potential milk-producing gland [39]. However, others have argued that the mechanism of inactivation might be different from that seen in inherited cases [41].

Summary of the invention

The present invention now reveals that the unusual high concentration of Alu-elements in the BRCA1 gene intronic regions [11] favors the induction of large genomic deletions and inversions in a situation of increased genomic instability although other mechanisms leading to these mutations may also play significant roles. The present invention

thus provides a diagnostic test kit (and means and methods) for determining mutations, especially deletions of relatively large stretches of nucleotides in genes associated with hereditary types of cancer, in particular such mutations (deletions of relatively large stretches of nucleotides) in the BRCA1 gene. Such mutations are difficult, if not impossible, to detect by the current[ly] PCR-based approach (if their occurrence or the site thereof is unknown) using genomic DNA as template, which has been most widely applied to establish the current mutation spectrum of BRCA1. - -

Please move he section entitled "**Brief description of the drawings**" which extends from page 14 onto page 15, to follow the section entitled "**Summary of the invention**" and precede the section entitled "**Detailed description of the invention**" at page 8.

In the claims

Please cancel claims 1-14 and add new claims 15-55 as follows:

15. (New) A diagnostic test kit for detecting the presence of or predisposition for breast cancer, wherein a means is provided for detecting a deletion of a stretch of nucleotides from a BRCA1 gene in a sample, wherein said deletion comprises at least a major part of any one or all of exons 13, 14, 15 and16, or at least a major part of exon 22.

16. (New) A diagnostic test kit according to claim 15, wherein the means comprises at least one probe for hybridization.

17. (New) A diagnostic test kit according to claim 15, wherein the means comprises the necessary elements for Southern blotting.

18. (New) A diagnostic test kit according to claim 16, wherein the probe comprises a sequence complementary to sequences on both sides of the deletion in the BRCA1 gene.

19. (New) A diagnostic test kit according to claim 17, wherein the necessary elements for Southern blotting comprises a probe, the probe comprising a sequence complementary to sequences on both sides of the deletion in the BRCA1 gene.

20. (New) A diagnostic test kit according to claim 15, wherein the deletion comprises all of one or more of exons 13, 14, 15, 16 or 22 of the BRCA1 gene.

21. (New) A diagnostic test kit according to claim 16, wherein the deletion comprises all of one or more of exons 13, 14, 15, 16 or 22 of the BRCA1 gene.

22. (New) A diagnostic test kit according to claim 17, wherein the deletion comprises all of one or more of exons 13, 14, 15, 16 or 22 of the BRCA1 gene.

23. (New) A diagnostic test kit according to claim 18, wherein the deletion comprises all of one or more of exons 13, 14, 15, 16 or 22 of the BRCA1 gene.

24. (New) A diagnostic test kit according to claim 19, wherein the deletion comprises all of one or more of exons 13, 14, 15, 16 or 22 of the BRCA1 gene.

25. (New) A diagnostic test kit according to claim 15, wherein the deletion comprises a frame shift and/or a termination codon.

26. (New) A diagnostic test kit according to claim 16, wherein the deletion comprises a frame shift and/or a termination codon.

27. (New) A diagnostic test kit according to claim 17, wherein the deletion comprises a frame shift and/or a termination codon.

28. (New) A diagnostic test kit according to claim 18, wherein the deletion comprises a frame shift and/or a termination codon.

29. (New) A diagnostic test kit according to claim 19, wherein the deletion comprises a frame shift and/or a termination codon.

30. (New) A diagnostic test kit according to claim 20, wherein the deletion comprises a frame shift and/or a termination codon.

31. (New) A diagnostic test kit according to claim 15, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

32. (New) A diagnostic test kit according to claim 16, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

33. (New) A diagnostic test kit according to claim 17, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

34. (New) A diagnostic test kit according to claim 18, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

35. (New) A diagnostic test kit according to claim 19, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

36. (New) A diagnostic test kit according to claim 20, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

37. (New) A diagnostic test kit according to claim 25, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

38. (New) A probe for use in a diagnostic test kit for detecting the presence of or predisposition for breast cancer, wherein a means is provided for detecting a deletion of a stretch of nucleotides from a BRCA1 gene in a sample, and wherein the deletion comprises at least a major part of any one or all of exons 13, 14, 15, and 16, or at least a major part of exon 22; said probe comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

39. (New) A probe for use in a diagnostic test kit according to claim 38, wherein the means comprises at least one probe for hybridization, the probe comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

40. (New) A probe for use in a diagnostic test kit according to claim 38, wherein the means comprises the necessary elements for Southern blotting, comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

41. (New) A probe for use in a diagnostic test kit according to claim 18, comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

42. (New) A probe for use in a diagnostic test kit according to claim 19 comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

43. (New) A probe for use in a diagnostic test kit according to claim 20 comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

44. (New) A probe for use in a diagnostic test kit according to claim 25 comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

45. (New) A probe for use in a diagnostic test kit according to claim 31 comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

46. (New) A probe for use in a diagnostic test kit according to claim 15, wherein the deletion comprises at least a major part of any one or all of exons 13, 14, 15, and 16, or at least a major part of exon 22 comprises, and wherein the probe is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

47. (New) A probe for use in a diagnostic test kit according to claim 16, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

48. (New) A probe for use in a diagnostic test kit according to claim 17, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

49. (New) A probe for use in a diagnostic test kit according to claim 18, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

50. (New) A probe for use in a diagnostic test kit according to claim 19, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

51. (New) A probe for use in a diagnostic test kit according to claim 20, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

52. (New) A probe for use in a diagnostic test kit according to claim 25, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

53. (New) A probe for use in a diagnostic test kit according to claim 31, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

54. (New) A probe for use in a diagnostic test kit according to claim 38, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

55. (New) A method of determining the presence in a sample of a nucleic acid derived from a BRCA1 gene having a deletion of a stretch of nucleotides, comprising contacting said sample with at least one probe which alone or together with a second means for detecting said deletion of a stretch of nucleotides from a BRCA1 gene, distinguishes between BRCA1 genes having said deletion and BRCA1 genes not

having said deletion, allowing hybridization between said probe and said nucleic acids to form a hybridization product and identifying the hybridization product, wherein said deletion comprises at least a major part of any one or all of exons 13, 14, 15, and 16, or at least a major part of exon 22.

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EXHIBIT 1

R'S Ninth New Collegiate Dictionary

A Merriam-Webster®

MERRIAM-WEBSTER INC., *Publishers*
Springfield, Massachusetts, U.S.A.

A GENUINE MERRIAM-WEBSTER

The name *Webster* alone is no guarantee of excellence. It is used by a number of publishers and may serve mainly to mislead an unwary buyer.

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Made in the United States of America

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The

English

A

Abbreviations

mail order *n* (1867) : an order for goods that is received and filled by mail

mail–order house *n* (1906) : a retail establishment whose business is conducted by mail

¹maim \'mām\ *vt* [ME *maynhen, maymen,* fr. OF *maynier*] (14c) **1** : to commit the felony of mayhem upon **2** : to mutilate, disfigure, or wound seriously — **maim-er** *n*

syn MAIM, CRIPPLE, MUTILATE, BATTER, MANGLE mean to injure so severely as to cause lasting damage. MAIM implies the loss or injury of a bodily member through violence; CRIPPLE implies the loss or serious impairment of an arm or leg; MUTILATE implies the cutting off or removal of an essential part of a person or thing thereby impairing its completeness, beauty, or function; BATTER implies a series of blows that bruise deeply, deform, or mutilate; MANGLE implies a tearing or crushing that leaves deep extensive wounds.

²maim *n* (14c) **1** *obs* : serious physical injury; *esp* : loss of a member of the body **2** *obs* : a serious loss

¹main \'mān\ *n* [in sense 1, fr. ME, fr. OE *mægen;* akin to OHG *magan* strength, OE *magan* to be able; in other senses, fr. ²*main* or by shortening — more at MAY] (bef. 12c) **1** : physical strength : FORCE — used in the phrase *with might and main* **2** **a** : MAINLAND **b** : HIGH SEA **3** : the chief part : essential point ⟨they are in the ~ well-trained⟩ **4** : a pipe, duct, or circuit which carries the combined flow of tributary branches of a utility system **5** **a** : MAINMAST **b** : MAINSAIL

²main *adj* [ME, fr. OE *mægen-,* fr. *mægen* strength] (bef. 12c) **1** : CHIEF, PRINCIPAL ⟨the ~ idea⟩ **2** : fully exerted : SHEER ⟨~ force⟩ ⟨by ~ strength⟩ **3** *obs* : of or relating to a broad expanse (as of sea) **4** : connected with or located near the mainmast or mainsail **5** : expressing the chief predication in a complex sentence ⟨the ~ clause⟩

Maine coon *n* (1935) : any of a breed of large long-haired domestic cats that have a very full tapered tail — called also *coon cat, Maine cat*

main-frame \'mān-ˌfrām\ *n* (1964) : a computer with its cabinet and internal circuits; *also* : a large fast computer that can handle multiple tasks concurrently

main-land \'mān-ˌland, -lənd\ *n* (14c) : a continent or the main part of a continent as distinguished from an offshore island or sometimes from a cape or peninsula — **main-land-er** \-ər\ *n*

¹main-line \'mān-ˈlīn\ *vt, slang* (1938) : to take by or as if by mainlining ~ *vi, slang* : to inject a narcotic drug (as heroin) into a principal vein

²main-line \'mān-ˌlīn\ *adj* (1941) : being part of an established group; *also* : being in the mainstream

main line *n* (1841) **1** : a principal highway or railroad line **2** *slang* : a principal vein of the circulatory system

main-ly \'mān-lē\ *adv* (13c) **1** *obs* : in a forceful manner **2** : for the most part : CHIEFLY

main-mast \'mān-ˌmast, -məst\ *n* (15c) : a sailing ship's principal mast usu. second from the bow

main-sail \'mān-ˌsāl, 'mān(t)-səl\ *n* (15c) : the principal sail on the mainmast — see SAIL illustration

main-sheet \'mān-ˌshēt\ *n* (15c) : a rope by which the mainsail is trimmed and secured

main-spring \'mān-ˌspriŋ\ *n* (1591) **1** : the chief spring in a mechanism esp. of a watch or clock **2** : the chief or most powerful motive, agent, or cause

main-stay \-ˌstā\ *n* (15c) **1** : a ship's stay extending from the maintop forward usu. to the foot of the foremast **2** : a chief support

main stem *n* (1832) : a main trunk or channel: as **a** : the main course of a stream **b** : the main line of a railroad **c** : the main street of a city or town

¹main-stream \'mān-ˌstrēm\ *n* (1831) : a prevailing current or direction of activity or influence — **mainstream** *adj*

²main-stream \'mān-'strēm\ *vt* (1974) : to place (as a handicapped child) in regular school classes

Main Street *n* (1598) **1** : the principal street of a small town **2** **a** : the sections of a country centering about its small towns **b** : a place or environment characterized by materialistic self-complacent provincialism — **Main Street-er** \'mān-ˌstrēt-ər\ *n*

main-tain \mān-'tān, mən-\ *vt* [ME *mainteinen,* fr. OF *maintenir,* fr. ML *manutenēre,* fr. L *manu tenēre* to hold in the hand] (14c) **1** : to keep in an existing state (as of repair, efficiency, or validity) : preserve from failure or decline ⟨~ machinery⟩ **2** : to sustain against opposition or danger : uphold and defend ⟨~ a position⟩ **3** : to continue or persevere in : CARRY ON, KEEP UP ⟨couldn't ~ his composure⟩ **4** **a** : to support or provide for : bear the expense of ⟨has a family to ~⟩ **b** : SUSTAIN ⟨enough food to ~ life⟩ **5** : to affirm in or as if in argument : ASSERT ⟨~ed that all men are not equal⟩ — **main-tain-abil-i-ty** \-ˌtā-nə-'bil-ət-ē\ *n* — **main-tain-able** \-'tā-nə-bəl\ *adj* — **main-tain-er** *n*

syn MAINTAIN, ASSERT, DEFEND, VINDICATE, JUSTIFY mean to uphold as true, right, just, or reasonable. MAINTAIN stresses firmness of conviction; ASSERT suggests determination to make others accept one's claim; DEFEND implies maintaining in the face of attack or criticism; VINDICATE implies successfully defending; JUSTIFY implies showing to be true, just, or valid by appeal to a standard or to precedent.

main-te-nance \'mānt-nən(t)s, -ᵊn-ən(t)s\ *n* [ME, fr. MF, fr. OF, fr. *maintenir*] (15c) **1** : the act of maintaining : the state of being maintained : SUPPORT **2** : something that maintains **3** : the upkeep of property or equipment **4** : an officious or unlawful intermeddling in a legal suit by assisting either party with means to carry it on

main-top \'mān-ˌtäp\ *n* (15c) : a platform about the head of the mainmast of a square-rigged ship

main–top-mast \'mān-'täp-ˌmast, -məst\ *n* (15c) : a mast next above the mainmast

main yard *n* (15c) : the yard of a mainsail

mair \'mār\ *chiefly Scot var of* MORE

mai-son-ette \ˌmāz-ᵊn-'et, ˌmās-\ *n* [F *maisonnette,* fr. OF, dim. of *maison* house, fr. L *mansion-, mansio* dwelling place — more at MANSION] (1793) **1** : a small house **2** : an apartment often on two floors

mai-tre d' *or* **mai-tre d'** \ˌmā-trə-'dē, ˌme-; ˌmāt-ər-'dē, ˌmet-\ *n, pl* **maître d's** *or* **maître d's** \-'dēz\ (1950) : MAÎTRE D'HÔTEL

mai-tre d'hô-tel \ˌmā-trə-(ˌ)dō-'tel, ˌme-; ˌmāt-dō-, ˌmet-\ *n, pl* **maîtres d'hôtel** *same*\ [F, lit., master of house] (1540) **1** **a** : MAJORDOMO **b** : HEADWAITER **2** : a sauce of butter, parsley, salt, pepper, and lemon juice — called also *maître d'hôtel butter*

maize \'māz\ *n* [Sp *maíz,* fr. Taino *mahiz*] (1555) : INDIAN CORN

ma-ja-gua \mə-'häg-wə\ *n* [AmerSp, fr. Taino] (ca. 1903) : either of two tropical trees of the mallow family that are often considered variant forms of a single species: **a** : an irregularly spreading or shrubby tree (*Hibiscus tilaceus*) that yields a light tough wood and a fibrous bast **b** : an erect forest tree (*H. elatus*) of the West Indian uplands that yields a moderately dense timber with variegated heartwood that is used esp. for cabinetwork and the stocks of guns

ma-jes-tic \mə-'jes-tik\ *adj* (1601) : having or exhibiting majesty : STATELY. *syn* see GRAND — **ma-jes-ti-cal-ly** \-ti-k(ə-)lē\ *adv*

maj-es-ty \'maj-ə-stē\ *n, pl* **-ties** [ME *maieste,* fr. MF *majesté,* fr. L *maj-estat-, majestas;* akin to L *major* greater] (14c) **1** : sovereign power, authority, or dignity **2** — used in addressing or referring to reigning sovereigns and their consorts ⟨Your *Majesty*⟩ ⟨Her *Majesty's* Government⟩ **3** **a** : royal bearing or aspect : GRANDEUR **b** : greatness or splendor of quality or character

ma-jol-i-ca \mə-'jäl-i-kə\ *also* **ma-iol-i-ca** \-'yäl-\ *n* [It *maiolica,* fr. ML *Majolica* Majorca, fr. LL *Majorca*] (1555) **1** : earthenware covered with an opaque tin glaze and decorated on the glaze before firing; *esp* : an Italian ware of this kind **2** : a 19th century earthenware modeled in naturalistic shapes and glazed in lively colors

¹ma-jor \'mā-jər\ *adj* [ME *maiour,* fr. L *major,* compar. of *magnus* great, large — more at MUCH] (14c) **1** : greater in dignity, rank, importance, or interest ⟨one of the ~ poets⟩ **2** : greater in number, quantity, or extent ⟨the ~ part of his work⟩ **3** : having attained majority **4** : notable or conspicuous in effect or scope : CONSIDERABLE ⟨a ~ improvement⟩ **5** : involving grave risk : SERIOUS ⟨a ~ illness⟩ **6** : of or relating to a subject of academic study chosen as a field of specialization **7** **a** : having half steps between the third and fourth and the seventh and eighth degrees ⟨~ scale⟩ **b** : based on a major scale ⟨~ key⟩ **c** : equivalent to the distance between the keynote and another tone (except the fourth and fifth) of a major scale ⟨~ third⟩ **d** : containing a major third ⟨~ triad⟩

²major *n* (1616) **1** : a person who has attained majority **2** **a** : one that is superior in rank, importance, size, or performance ⟨economic power of the oil ~s⟩ **b** : a major musical interval, scale, key, or mode **3** : a commissioned officer in the army, air force, or marine corps ranking above a captain and below a lieutenant colonel **4** **a** : a subject of academic study chosen as a field of specialization **b** : a student specializing in such a field ⟨he is a history ~⟩ **5** *pl* : major league baseball

³major *vi* **ma-jored; ma-jor-ing** \'māj-(ə-)riŋ\ (1913) : to pursue an academic major

major axis *n* (1854) : the axis passing through the foci of an ellipse

ma-jor-do-mo \ˌmā-jər-'dō-(ˌ)mō\ *n, pl* **-mos** [Sp *mayordomo* or obs. It *maiordomo,* fr. ML *major domus,* lit., chief of the house] (1589) **1** : a head steward of a large household (as a palace) **2** : BUTLER, STEWARD **3** : a person who speaks, makes arrangements, or takes charge for another

ma-jor-ette \ˌmā-jə-'ret\ *n* (1940) : DRUM MAJORETTE 2

major general *n* [F *major général,* fr. *major,* n: + *général,* adj., general] (1642) : a commissioned officer in the army, air force, or marine corps who ranks above a brigadier general and whose insignia is two stars

ma-jor-i-tar-i-an \mə-ˌjȯr-ə-'ter-ē-ən, -ˌjär-\ *n* (1942) : one that believes in or advocates majoritarianism — **majoritarian** *adj*

ma-jor-i-tar-i-an-ism \-ē-ə-ˌniz-əm\ *n* (1942) : the philosophy or practice according to which decisions of an organized group should be made by a numerical majority of its members

ma-jor-i-ty \mə-'jȯr-ət-ē, -'jär-\ *n, pl* **-ties** (1552) **1** *obs* : the quality or state of being greater **2** **a** : the age at which full civil rights are accorded **b** : the status of one who has attained this age **3** **a** : a number greater than half of a total **b** : the excess of a majority over the remainder of the total : MARGIN **c** : the preponderant quantity or share **4** : the group or political party whose votes preponderate **5** : the military office, rank, or commission of a major — **majority** *adj*

majority leader *n* (1952) : a leader of the majority party in a legislative body (as the U.S. Senate)

majority rule *n* (1893) : a political principle providing that a majority usu. constituted by fifty percent plus one of an organized group will have the power to make decisions binding upon the whole

major league *n* (1906) **1** : a league of highest classification in U.S. professional baseball; *broadly* : a league of major importance in any of various sports **2** : BIG TIME 2

major–medical *adj* (ca. 1955) : of, relating to, or being a form of insurance designed to pay all or part of the medical bills of major illnesses usu. after deduction of a fixed initial sum

major order *n* (ca. 1727) : one of the Roman Catholic or Eastern clerical orders that are sacramentally conferred and have a sacred character that implies major religious obligations (as clerical celibacy) — usu. used in pl.; compare MINOR ORDER

major party *n* (1950) : a political party having electoral strength sufficient to permit it to win control of a government usu. with comparative regularity and when defeated to constitute the principal opposition to the party in power

major penalty *n* (ca. 1936) : a 5-minute suspension of a player in ice hockey

major premise *n* (1860) : the premise of a syllogism containing the major term

major seminary *n* (1945) : a Roman Catholic seminary giving usu. the entire six years of senior college and theological training required for major orders

major suit *n* (1916) : either of two bridge suits of superior scoring value: **a** : SPADES **b** : HEARTS

major term *n* (1860) : the term of a syllogism constituting the predicate of the conclusion

ma-jus-cule \'maj-əs-ˌkyü(ə)l, mə-'jəs-\ *n* [F, fr. L *majusculus* rather large, dim. of *major*] (1727) : a large letter (as a capital) — **ma-jus-cu-lar** \mə-'jəs-kyə-lər\ *adj* — **majuscule** *adj*

mak-able *or* **make-able** \'mā-kə-bəl\ *adj* (15c) : capable of being made

mak-ar \'mäk-ər, 'māk-\ *n* [ME *maker*] *chiefly Scot* (14c) : POET

¹make \'māk\ *vb* **made** \'mād\; **mak-ing** [ME *maken,* fr. OE *macian;* akin to OHG *mahhōn* to prepare, make, OSlav *mazati* to anoint] (bef. 12c) **1** **a** *obs* : BEHAVE, ACT **b** : to seem to begin (an action) ⟨*made* to go⟩ **2** **a** : to cause to happen to or be experienced by ⟨*made* trouble for us⟩ **b** : to cause to exist, occur, or appear : CREATE ⟨~ a disturbance⟩ **c** : to favor the growth or occurrence of ⟨haste ~s waste⟩ **d** : to fit, intend, or

⟨*made* to be an actor⟩ **3** **a** : to ... or altering material : FASHION ⟨... verses⟩ **c** : to lay out and construct ... mulate in the mind ⟨~ plans⟩ ... : CONSTITUTE ⟨houses *made* of st... ~ **b** : to form and hold in the ... assemble and set alight the mate... fuels⟩ **c** : PREPARE, FIX ⟨~ dinn... preparation for dealing **8** : to ... storing **9** **a** : to cause to be or ... POINT ⟨*made* him bishop⟩ **10** ... execute in an appropriate manner ... **11** **a** *chiefly dial* : SHUT ⟨the do... to cause (an electric circuit) to ... to the nature or meaning of som... actions⟩ **b** : to regard as being ⟨... carry out (an action indicated or ... speech⟩ **b** : to perform with a ... ture⟩ **c** : to achieve by traversi... **14** **a** : to produce as a result of ... to something ⟨~ a mess of the jo... *archaic* : to turn into another lan... act in a certain way : COMPEL ⟨~ ... assure the success or prosperity o... **17** **a** : to amount to in signific... form the essential being of ⟨clot... assembling of individuals ⟨~ a q... third time he's said it⟩ **18** **a** : t... fashioned into ⟨rags ~ the best p... a fine judge⟩ **c** : FORM 5b **19** ... you'll never ~ it that far⟩ **b** : ... gain a place on or in ⟨~ the team ... gain (as money) by working, tra... ; to act so as to win or acqui... (points) in a game or sport **c** ... bowling **22** **a** : to fulfill (a co... trick with (a card) **23** **a** : to in... York on the return trip⟩ **b** : CAT... ; to persuade to consent to sexu... vide the most enjoyable or satisfy... the show really *made* our day⟩ ~ ... ¹ BEHAVE, ACT **b** : to begin or s... though to hand it to me⟩ **c** : to... cherry⟩ **d** *slang* : to play a part ... HEAD ⟨*made* after the fox⟩ ⟨*made* ... height or size ⟨the tide is *makin*... certain direction **6** : to have we... safer driving⟩ **7** : to undergo m... up beautifully⟩

syn MAKE, FORM, SHAPE, FASHION mean to cause to come into being whether by an intelligent agent or immaterial or immaterial existence; FORM ... ture, or design in the thing pr... form upon some material; FASHION ... or ingenuity; FABRICATE suggests ... often implies an ingenious in... TURE implies making repeatedly ... chinery; FORGE implies a making ... tal effort.

make a face : to distort one's ... **make out of a molehill** : to treat a ... **make away with** **1** : to carry ... LIFE **4** : CONSUME, EAT — **make b...** VENTURE, DARE — **make book** : ... all the entrants in a race or conte... with the means at hand — **m...** adequate to one's needs — **make ...** an object of amusement or laught... to make valid or complete: as ... INDEMNIFY ⟨*make good* the loss⟩ ... good his promise⟩ ⟨*made good* th... charge⟩ **2** : to prove to be capa... make use of offered opportunity ... **make head** **1** : to make progress ... formed revolt **3** : to build up pres... **4** : to be successful ⟨trying to *ma...* ... tographer —Joe Kane⟩ **2** : to ha... to treat as of little account — ... NECK, PET **b** : to engage in sex ... to treat as of importance **2** : t... ... consideration — **make no bon...** ... or sure ⟨*makes no bones* about ... **make public** : DISCLOSE — **make s...** ... out on a voyage — **make spe...** **grade** : to measure up to some s... **make out of** : to show or use to the be... : to be present at or participate in ... **make time** **1** : to travel fast **2** : ... toward winning favor ⟨trying to *m...* **tracks** **1** : to proceed at a walk ... **away** : FLEE — **make use of** : to p... of a boat : LEAK **2** : URINATE — ... **entrance** — **make way** **1** : to giv... ... crying **2** : to make progress — ... usu. used with *the*

make *n* (14c) **1** **a** : the manner ... constructed **b** : BRAND 4a **2** : the pl... of a person ⟨men of his ~ are ra... manufacturing **b** : the actual pie... ... period : OUTPUT **4** : the deck ... bridge **5** : the closing or comple... of shuffling cards; *also* : turn to